Commentary

Genetic Markers in Huntington's Disease

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Huntington's disease is a neurodegenerative disorder that is inherited as an autosomal dominant trait. It is typically expressed later in a patient's adult years, when it may have already been transmitted to the patient's children. The clinical symptoms of this disorder include a progressive dementia combined with extrapyramidal motor manifestations of the choreoathetotic type. Huntington's disease has as its most prominent neuropathologic feature a notable atrophy of the caudate nucleus, which is accompanied by less severe degeneration in the putamen, globus pallidus and the cerebral cortex. Studies have shown that patients with Huntington's disease have alterations in striatal receptors for γ-aminobutyric acid (GABA), benzodiazepines, muscarinic cholinergics, cholecystokinin and dopamine. Such changes have been related to some extent to the loss of local circuit cholinergic and GABAergic neurons as well as those neurons that project from the striatum to other portions of the basal ganglia. A reduction in feedback inhibition of dopaminergic cells in the substantia nigra may lead to augmented dopaminergic activity in the striatum, a putative precondition in the development of the choreoathetosis characteristic of the disease.

Recently, a DNA sequence probe called G8 has been identified and has been shown to be closely linked to the Huntington's disease gene on chromosome 4. This new marker is a 17.6-kilobase fragment of DNA that after digestion with the bacterial restriction enzyme, Hind III, can give rise to one of four fragments or polymorphisms. These haplotypes are called A, B, C and D. The discovery of the localization of a restriction fragment length polymorphism linked to the Huntington's disease gene constitutes the first use of recombinant DNA technology to locate a gene without having any previous knowledge regarding gene location.

The use of this marker for the purpose of prediction tests in persons at risk represents a great advance in our ability to unmask the predisposition to a complex hereditary disease. Unfortunately, in the use of the G8 marker, the sequence is not close enough to the gene so that one haplotype invariably segregates with the presence of Huntington's disease. For this reason an error rate due to genetic recombination of 5% to 10% occurs even when a sufficient number of family members is available for study. Ideally, both the grandparents and parents of a person at risk should be available for analysis of the G8 marker. An additional caveat in the use of this marker for prediction testing in Huntington's disease is that the onset of the disorder is late enough in life that some of the parents and grandparents will probably be deceased.

The use of prediction testing involves two principal components: marker identification and pedigree analysis. In the most elementary and informative case, information is available from three generations: the grandparents, the parents and the person at risk. Prediction is more difficult when information from only two generations is available. An additional confounder in the prediction test is the possible error caused by recombination between the marker and the locus of the Huntington's disease gene.

An example of the process of genetic analysis will illustrate the use of the probe. In the best of circumstances wherein the grandparents and parents are alive, an affected parent might have received the Huntington's disease gene and the A marker haplotype from one of the affected grandparents, the other grandparent and parent being unaffected and labeled BB and CC, respectively. If the child also received an A marker, then in the absence of recombination this person at risk would be expected to be affected and hence labeled AC or AB. If the person at risk were BC, then, also barring the possibility of recombination, this person would be expected to be normal. It is important to point out that the A, B, C, D haplotypes represent only labels for polymorphism. Any one family may have associated with it any of the four labels. Moreover, the significance of such polymorphisms in the marking of the disease state concerns the presence of one of these haplotypes in conjunction with the affected person. It then becomes likely that, barring errors of recombination, offspring with the disease-associated haplotype will be afflicted with the disease.

At present additional markers are being generated to flank and, ultimately, converge on the Huntington's disease gene itself. The addition of these new markers serves to increase heterozygosity and thereby provide more precise counseling because a greater pattern complexity allows us to better distinguish between persons.

The development of a testing procedure for a disease that is lethal, of late onset and for which there is no current treatment is not without significant controversy. For instance, there is speculation that in those who test positive there will be an escalated risk of suicide, psychiatric manifestations, substance abuse, divorce and employment problems, to name just a few. The development of these testing procedures, however, will begin to assume greater importance when the prospects of early diagnosis will contribute to optimizing the potency of forthcoming treatment stratagems. In essence, these new findings represent a major advance toward the progression of steps that will lead to the understanding, treatment and prevention of hereditary disorders such as Huntington's disease. Finally, despite the considerable limitations of the current testing procedures, there is confidence that over the next five to ten years, gene isolation techniques will become available so that all suspected persons can be tested regardless of which relatives are available for pedigree analysis.

GENERAL REFERENCES

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